Therapeutic Apheresis and Dialysis

Therapeutic Apheresis and Dialysis 2013; 17(1):40–47
doi: 10.1111/j.1744-9987.2012.01130.x

Survey of the Effects of a Column for Adsorption of β2-Microglobulin in Patients With Dialysis-Related Amyloidosis in Japan

Fumitake Gejyo,[1] Izumi Amano,[2] Tetsuo Ando,[3] Mari Ishida,[4] Seiichi Obayashi,[5] Hiroshi Ogawa,[6] Toshihiko Ono,[7] Yutaka Kanno,[8] Tateki Kitaoka,[9] Kazutaka Kukita,[10] Satoshi Kurihara,[11] Motoyoshi Sato,[12] Jeongsoo Shin,[13] Masashi Suzuki,[14] Susumu Takahashi,[15] Yoshio Taguma,[16] Yoshiaki Takemoto,[17] Ryoichi Nakazawa,[18] Takeshi Nakanishi,[19] Hidetoshi Nakamura,[20] Shigeko Hara,[21] Makoto Hiramatsu,[22] Ryuichi Furuya,[23] Ikuto Masakane,[24] Kenji Tsuchida,[25] Yasuki Motomiya,[26] Hiroyuki Morita,[27] Kunihiro Yamagata,[28] Kunihiko Yoshiya,[29] and Tomoyuki Yamakawa[30] (The Society of β2-Microglobulin Adsorption Therapy)

[1]Office of the President, Niigata University, Niigata; [2]Nagoya Vascular Access Amano Memorial Clinic, Nagoya; [3]Department of Dialysis and Kidney Transplantation, Hidaka Hospital, Takasaki; [4]Department of Internal Medicine, Kitasaito Hospital, Asahikawa; [5]Kinashi Obayashi Hospital, Takamatsu; [6]Shinseikai Dai-ichi Hospital, Nagoya; [7]Tojinkai Hospital, Kyoto; [8]Kanno Dialysis & Vascular Access Clinic, Matsumoto; [9]Bousei Hospital, Saitama; [10]Department of Surgery, Sapporo Hokuyu Hospital, Sapporo; [11]Saitama Tsukinomori Clinic, Saitama; [12]Department of Nephrology and Dialysis Therapy, Social Insurance Chukyo Hospital, Nagoya; [13]Motomachi HD Clinic, Kobe; [14]Shinrakuen Hospital, Niigata; [15]Nihon University Graduate School, Tokyo; [16]Sendai Shakai Hoken Hospital, Sendai; [17]Departments of Artificial Kidney, Osaka City University School of Medicine, Osaka; [18]Tokatsu-Clinic, Matsudo, [19]Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya; [20]Kokura Daiichi Hospital, Kokura; [21]Toranomon Hospital, Minato-ku; [22]Center for Kidney and Diabetic Diseases, Okayama Saiseikai General Hospital, Okayama; [23]Department of Internal Medicine, Iwata City Hospital, Iwata; [24]Yabuki Shima Clinic, Yamagata; [25]Department of Kidney Disease, Kawashima Hospital, Tokushima; [26]Suiyukai Clinic, Kashihara; [27]Morita Clinic, Nagoya; [28]Department of Nephrology, Division of Clinical Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba; [29]Hara Genitourinary Hospital, Kobe; and [30]Shirasagi Hospital, Osaka, Japan

Abstract: Dialysis-related amyloidosis is a serious complication of long-term hemodialysis. Its pathogenic mechanism involves accumulation of β2-microglobulin in the blood, which then forms amyloid fibrils and is deposited in tissues, leading to inflammation and activation of osteoclasts. Lixelle, a direct hemoperfusion column for adsorption of β2-microglobulin, has been available since 1996 to treat dialysis-related amyloidosis in Japan. However, previous studies showing the therapeutic efficacy of Lixelle were conducted in small numbers of patients with specific dialysis methods. Here, we report the results of a nationwide questionnaire survey on the therapeutic effects of Lixelle. Questionnaires to patients and their attending physicians on changes in symptoms of dialysis-related amyloidosis by Lixelle treatment were sent to 928 institutions that had used Lixelle, and fully completed questionnaires were returned from 345 patients at 138 institutions. The patients included 161 males and 184 females 62.9 ± 7.7 years age, who had undergone dialysis for 25.9 ± 6.2 years and Lixelle treatment for 3.5 ± 2.7 years. Based on self-evaluation by patients, worsening of symptoms was inhibited in 84.9–96.5% of patients. Of the patients, 91.3% felt that worsening of their overall symptoms had been inhibited, while attending physicians evaluated the treatment as effective or partially effective for 72.8% of patients. Our survey showed that Lixelle treatment improved symptoms or prevented the progression of dialysis-related amyloidosis in most patients. **Key Words:** β2-microglobulin, Adsorption column, Dialysis-related amyloidosis, Lixelle, Questionnaire survey.

Received April 2012; revised July 2012.
Address correspondence and reprint requests to Professor Fumitake Gejyo, President of Niigata University, 8050 Ikarashi 2-no-cho, Nishi-ku, Niigata 950-2181, Japan. Email: gejyo@med.niigata-u.ac.jp

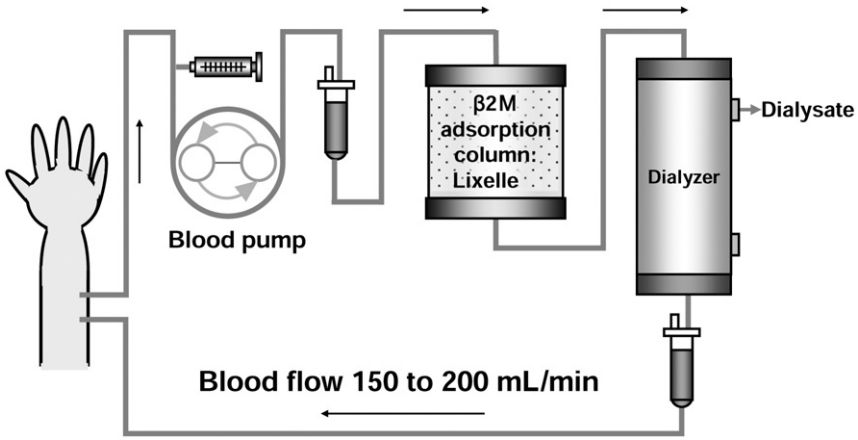

FIG. 1. Circuit diagram; sequential use of Lixcelle.

β2 microglobulin (β2M) was found to be a major pathogenic factor for dialysis-related amyloidosis (DRA) in 1985 (1). β2M is produced in most cells throughout the body and is metabolized in the kidney in healthy individuals. However, in HD patients with renal dysfunction, β2M accumulates excessively in the blood and forms amyloid fibrils that are then deposited in bones, joints, and soft tissues. These fibrils are further modified by advanced glycation end products (AGE), inducing local macrophage infiltration and production of cytokines and chemokines (2–6). This leads to severe complications with various inflammatory diseases, which are collectively referred to as DRA (7–10).

Lixelle is a direct hemoperfusion column that was developed to selectively adsorb and eliminate β2M from the blood of patients with DRA (11). It is connected in series to the dialyzer on a HD circuit to treat DRA patients at each dialysis session (Fig. 1). Porous cellulose beads with covalently linked hexadecyl alkyl chain ligands are packed in 350-mL, 250-mL, or 150-mL columns. These selectively adsorb hydrophobic peptides with a molecular weight <20 kD, including β2M, via a molecular sieving effect because of its porous structure and hydrophobic interaction with ligands (11,12). Lixelle has been used to relieve symptoms and prevent the progression of DRA since 1996, when health insurance coverage and reimbursement for Lixelle treatment were approved by Japanese Ministry of Health, Labour, and Welfare. It is approved for treatment of patients who meet all of the following three criteria: (i) β2M-based amyloid deposition found during surgery or on biopsy; (ii) dialysis for ≥10 years with carpal tunnel release, and (iii) bone cyst found on diagnostic imaging (13).

Lixelle treatment has been shown to prevent the progression of DRA in regular HD, improve the activities of daily living (ADL), and suppress the formation of advanced bone cysts (14,15). In another study, one year of Lixelle treatment decreased blood β2M concentrations, improved visual analog scale (VAS) scores for arthralgia and ADL, enabled recovery of distal latency of the median nerve (associated with carpal tunnel syndrome) to the normal range, and increased pinch strength (13). However, these findings were based on epidemiological studies without a detailed protocol for DRA diagnosis and studies on relatively small numbers of patients undergoing specific types of dialysis. The results therefore do not reflect the diversity of symptoms and the variety of HD membranes used in clinical practice. Therefore, the Society of β2-Microglobulin Adsorption Therapy decided to examine the effects of Lixelle treatment in the first nationwide survey of Japanese patients diagnosed with DRA by using defined criteria.

PATIENTS AND METHODS

This questionnaire survey was conducted between December 2007 and April 2008. The subjects were DRA patients with an immunohistopathologically confirmed diagnosis of β2M amyloidosis who met all three criteria for Lixelle treatment (described below) and had been receiving treatment for at least 9 months. Lixelle treatment was used for patients who fulfilled all the following criteria: (i) β2M-based amyloid deposition revealed by Congo red staining and immunostaining of tissue samples obtained from lesions at surgery for carpal tunnel syndrome or on biopsy; (ii) dialysis for ≥10 years and carpal tunnel release; and (iii) the presence of bone cysts in their joints, confirmed by X-ray imaging. The patients' attending physicians were also asked to respond to the survey. Questionnaires were sent to 928 institutions with records of treatment using the Lixelle

column. A total of 345 patients and their attending physicians at 138 of 928 institutions, which cooperated with the survey, returned fully completed questionnaires.

Questionnaire

The patients and attending physicians were asked about background factors and quality of life (QOL) in order to compare the symptoms before the start of Lixelle treatment with current symptoms.

(1) Questions to patients:

The following questions (i–vi) were asked to survey the patients' subjective self-evaluation of any change in the symptoms caused by the treatment. Restrictions affecting daily activities were investigated using eight items based on the Stanford Health Assessment Questionnaire (HAQ) (16). Questions were asked by a nurse for patients who had poor eyesight.

(i) Comparison of overall symptoms before Lixelle treatment and at the time of the survey: evaluated as "Improved," "Unchanged," or "Worsened"
(ii) VAS score for current arthralgia (0–10, corresponding to no pain to severe pain)
(iii) Frequency of waking due to pain each night
(iv) Comparison of arthralgia, arthralgia in bed, number of joints with arthralgia, limitation of joint motion, finger stiffness and numbness, and frequency of waking due to pain each night before Lixelle treatment and at the time of the survey: evaluated as "Decreased," "Unchanged," or "Increased"
(v) Comparison of the dose of oral analgesics before Lixelle treatment and at the time of the survey: evaluated as "Decreased," "Unchanged," or "Increased"
(vi) Evaluation of the number of restricted daily activities

Patients selected all that applied from the following eight items picked from the HAQ.

(a) "Turn faucets on and off?"
(b) "Dress yourself, including shoelaces and buttons?"
(c) "Lift a full cup or glass to your mouth?"
(d) "Shampoo your hair?"
(e) "Get in and out of bed?"
(f) "Walk outdoors on flat ground?"
(g) "Bend down to pick up clothing from the floor?"
(h) "Climb up 5 steps?"

(2) Questions to physicians:

Physicians were asked to evaluate the clinical effects of Lixelle treatment on their patients as "Effective," "Partially effective," or "Ineffective." Physician evaluations were performed by comparing each patient's overall condition on the basis of objective records such as patient complaints, mobility, and doses of oral analgesics before Lixelle treatment and at the time of the survey.

TABLE 1. *Background factors of patients surveyed regarding dialysis-related amyloidosis in Japan*

Number of patients (M : F)	345 (161:184)
Age (years)	62.9 ± 7.7
Treatment history (years)	
Hemodialysis	25.9 ± 6.2
Treatment with Lixelle	3.5 ± 2.7
VAS score for arthralgia	
All patients (345)	5.0 ± 3.1
Patients with VAS > 0 (287)	6.0 ± 2.3
Night-time awakening (times/one night)	1.1 ± 2.2
Primary disease (number of patients [%])	
Chronic glomerulonephritis	279 (80.9%)
Diabetic nephropathy	5 (1.4%)
Nephrosclerosis	4 (1.2%)
Polycystic kidney disease	3 (0.9%)
Other disease	54 (15.6%)

Age, treatment history, VAS (visual analog scale) score, and night-time awakening are shown as mean ± standard deviation (SD).

Statistical analysis

Comparison of data between patient groups was performed using the Student's *t*-test, and correlations were determined using Pearson's correlation coefficient. *P*-values less than 0.05 were considered significant.

RESULTS

The backgrounds of 345 patients are shown in Table 1. The mean dialysis period was 25.9 ± 6.2 years and ranged from 10 to 38 years. The mean period of Lixelle treatment was 3.5 ± 2.7 years, with a range from 9 months to 11 years. In all patients, Lixelle treatment had been applied to improve DRA-related symptoms that had not been improved by treatment with a high-flux membrane dialyzer alone. The primary disease was chronic glomerulonephritis in 80.9% of cases and diabetic nephropathy in 1.4%. The mean VAS score for arthralgia in all patients was 5.0 ± 3.1. At the time of the survey, 58 patients had no arthralgia (VAS score = 0) and 287 had arthralgia with a mean VAS score of 6.0 ± 2.3. The dialysis periods of patients with (VAS score > 0) and without (VAS score = 0) arthralgia were 26.1 ± 6.2 and 24.6 ± 6.3 years, respectively ($P = 0.09$), and the periods of Lixelle treatment were

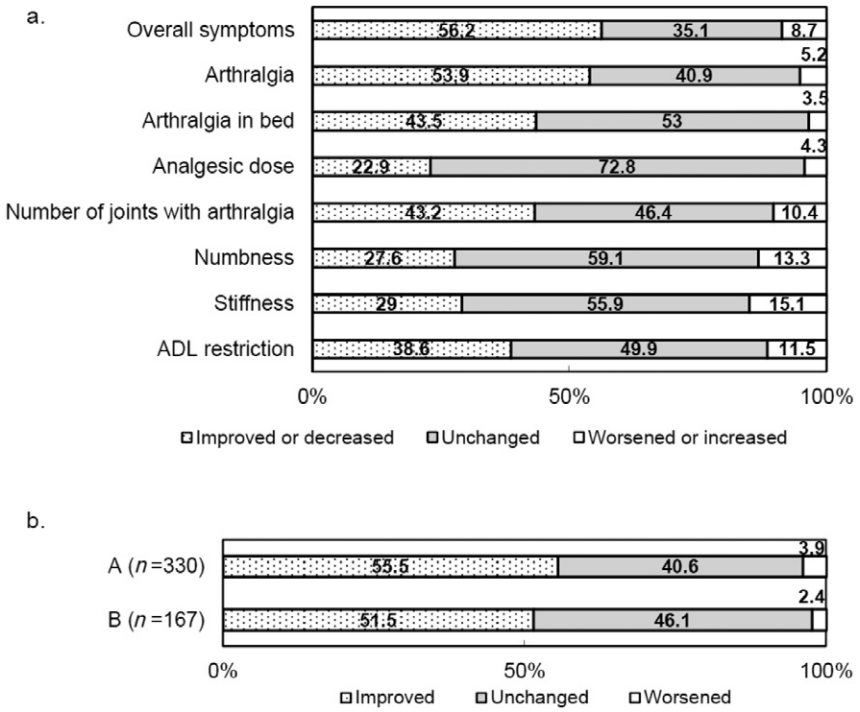

FIG. 2. (a) Changes in dialysis-related amyloidosis (DRA) symptoms and analgesic doses ($n = 345$). (b) Changes in arthralgia (A) in patients given analgesics at lower or unchanged doses and (B) in patients without a history of analgesic treatment. ADL, activities of daily living.

3.7 ± 2.7 and 3.0 ± 2.4 years, respectively, with no significant differences between the groups ($P = 0.10$). Therefore, there was no significant correlation between the VAS score and the period of dialysis or Lixelle treatment. The mean frequency of night-time awakening due to pain was 1.1 ± 2.2 times each night.

The percentages of patients with restriction for each item of daily activities were 29.6% for "Turn faucets on and off"; 54.2% for "Dress yourself, including shoelaces and buttons"; 17.7% for "Lift a full cup or glass to your mouth"; 18.0% for "Shampoo your hair"; 38.8% for "Get in and out of bed"; 23.2% for "Walk outdoors on flat ground"; 48.1% for "Bend down to pick up clothing from the floor"; and 52.2% for "Climb up 5 steps". Patients experienced more difficulty in activities associated with leg motion and whole-body motion than those involving hands and arms alone.

The patients' responses regarding changes in the DRA symptoms and doses of oral analgesics from the start of Lixelle treatment until the time of the survey (mean: 3.5 ± 2.7 years) are shown in Figure 2a. Regarding overall symptoms, 56.2%, 35.1%, and 8.7% patients felt that these had improved, not changed, and worsened, respectively. Among the symptoms, arthralgia was perceived to have improved the most, with 53.9%, 40.9%, and 5.2% of the patients indicating improvement, no change, and worsening, respectively. There were also perceived improvements in arthralgia in bed, the number of joints with arthralgia, and joint motion limitations. The doses of analgesics had decreased, were unchanged (including no administration), and had increased in 22.9%, 72.8%, and 4.3% of the patients, respectively. Of the 330 patients with decreased or unchanged (including no administration) doses of analgesics, 55.5%, 40.6%, and 3.9% felt that arthralgia had improved, not changed, and worsened, respectively. Of the 167 patients who did not take analgesics, 51.5%, 46.1%, and 2.4% felt that arthralgia had improved, not changed, and worsened, respectively (Fig. 2b).

The physicians' evaluation indicated that Lixelle treatment was "Effective" in 251 (72.8%) patients, "Partially effective" in 83 (24.1%), and "Ineffective" in 11 (3.2%) (Fig. 3). Of the 251 cases in which treatment was evaluated as "Effective" by physicians, 181 (72.1%), 60 (23.9%), and 10 (4.0%) of the patients felt that symptoms had improved, not changed, and worsened, respectively. Of the 83 cases in which treatment was evaluated as "Partially effective" by physicians, 12 (14.5%), 53 (63.9%), and 18 (21.7%) of the patients felt that symptoms had improved, not changed, and worsened, respectively (Fig. 3).

Table 2 shows the profiles of patients grouped by their answers regarding changes in DRA symptoms before and after Lixelle treatment (Improved,

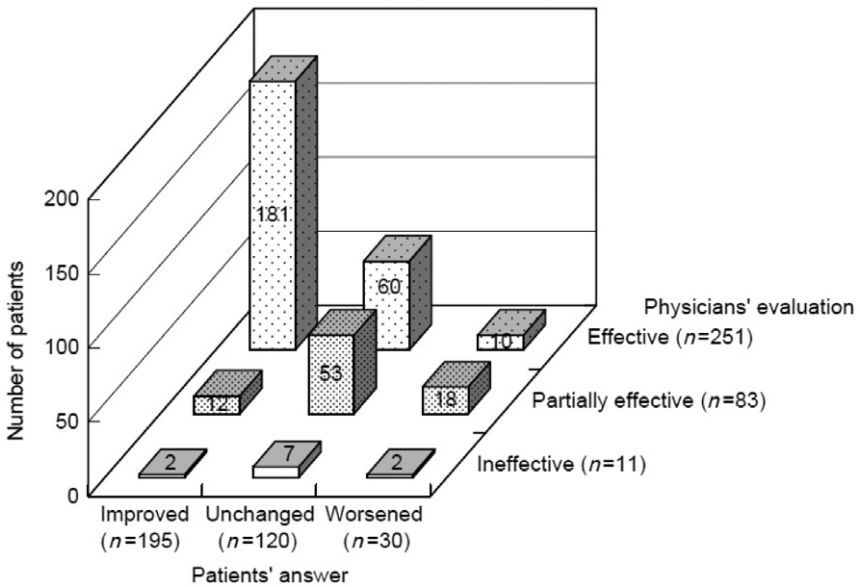

FIG. 3. Comparison between physician's evaluation of the effect of Lixelle treatment (Effective, Partially effective, and Ineffective) and patient's answer regarding change in overall symptoms before to after Lixelle treatment (Improved, Unchanged, and Worsened).

Unchanged, and Worsened). Table 3 shows the profiles of the patients grouped by physicians' evaluations of the effect of Lixelle treatment on their patients (Effective, Partially effective, and Ineffective). The mean dialysis periods of the groups of "Improved" and "Unchanged" patients were significantly shorter than those of the "Worsened" patients. The mean dialysis periods of patient groups with physician evaluations of "Effective" or "Partially effective" were similarly shorter than those of the patients in the "Ineffective" group. The mean periods of Lixelle treatment in the "Improved" and "Unchanged" groups were significantly shorter than those in the "Worsened" group. In contrast, the mean period of Lixelle treatment in the patient groups with physician evaluations of "Effective" or "Partially effective" were longer than those in the "Ineffective" group.

DISCUSSION

In 1998, a Japanese Society for Dialysis Therapy (JSDT) survey found that DRA patients accounted for 31.0% of the 185 322 HD patients and that patients who had undergone dialysis for at least 25 years accounted for 90.0% of the DRA patients (17). A JSDT report covering 2007–2008 showed that diabetic nephropathy was the main primary disease in HD patients, with a frequency of 43.2%, followed by chronic glomerulonephritis at 23.0%; in contrast, a 1985 report indicated rates of 19.6% and 56.0%, respectively, for these diseases. However, in our survey, the mean dialysis period was 25.9 years and the primary disease was chronic glomerulonephritis, which was present in 80.9% of the patients. The low percentage of patients with diabetic nephropathy in

TABLE 2. *Background factors of patients grouped by patient's answer regarding change in overall symptoms before to after Lixelle treatment (Improved, Unchanged, and Worsened)*

	Patient's answer		
	Improved	Unchanged	Worsened
Number of patients (M : F)	194 (82:112)	121 (61:60)	30 (18:12)
Age (years)	63.0 ± 7.8	63.1 ± 7.6	61.1 ± 8.1
Dialysis period (years)	25.7 ± 6.0***	25.5 ± 6.6**	28.5 ± 5.2***.**
Age at start of Lixelle treatment (years)	59.6 ± 8.4***	60.0 ± 8.6**	55.9 ± 8.3***.**
Dialysis period at start of Lixelle treatment (years)	22.4 ± 5.7	22.2 ± 6.1	23.7 ± 4.7
Duration after start of Lixelle treatment (years)	3.5 ± 2.5***	3.2 ± 2.7**	5.2 ± 2.8***.**
VAS score for arthralgia	4.4 ± 3.1*.***	5.5 ± 3.0*.**	6.7 ± 2.2***.**
Nighttime awakening (times/one night)	1.1 ± 2.6	1.0 ± 1.5**	1.9 ± 2.0**
Number of restricted ADL items	2.6 ± 2.2***	2.8 ± 2.2**	4.3 ± 2.0***.**

*Improved vs. Unchanged: $P < 0.05$, **Unchanged vs. Worsened: $P < 0.05$, ***Improved vs. Worsened: $P < 0.05$, the Student *t*-test. Age, treatment history, VAS (visual analog scale) score, nighttime awakening, and number of restricted activities of daily living (ADL) items were shown as mean ± standard deviation (SD).

TABLE 3. *Background factors of patients grouped by physician's evaluation of the effect of Lixelle treatment (Effective, Partially effective, and Ineffective)*

	Physician's evaluation		
	Effective	Partially effective	Ineffective
Number of patients (M : F)	251 (107:144)	83 (49:34)	11 (5:6)
Age (years)	62.9 ± 7.8	62.7 ± 7.8	64.0 ± 7.6
Dialysis period (years)	25.5 ± 6.3	26.7 ± 5.9	27.5 ± 6.7
Age at start of Lixelle treatment (years)	59.4 ± 8.6	59.1 ± 8.3	61.3 ± 9.0
Dialysis period at start of Lixelle treatment (years)	22.1 ± 5.9	23.3 ± 5.3	24.5 ± 5.8
Duration after start of Lixelle treatment (years)	3.6 ± 2.5	3.6 ± 2.9	2.7 ± 2.5
VAS score for arthralgia	4.6 ± 3.1*,***	5.8 ± 2.7*	6.7 ± 2.8***
Nighttime awakening (times/one night)	1.1 ± 2.5	1.2 ± 1.5	0.8 ± 1.2
Number of restricted ADL items	2.7 ± 2.2***	3.1 ± 2.4	4.1 ± 2.3***

*Effective vs. Partially effective: $P < 0.05$, **Partially effective vs. Ineffective: $P < 0.05$, ***Effective vs. Ineffective: $P < 0.05$, the Student *t*-test. Age, treatment history, VAS (visual analog scale) score, nighttime awakening, and number of restricted activities of daily living (ADL) items were shown as mean ± standard deviation (SD).

the current survey appears to reflect the distribution of primary diseases at the time the participants began dialysis, and this may be partly due to the poor prognosis of this disease.

Dialysis-related amyloidosis is a progressive disease for which no cure exists except renal transplantation; it is therefore important to inhibit the progression of disease by preventing further amyloid deposition. In 1999, the JSDT conducted a survey in 1196 patients with newly developed DRA and found that the risk of worsening within 1 year following the development of DRA in patients who had undergone HD for ≥20 to <25 years was 2.69 times higher than that in patients who had undergone HD for ≥5 to <10 years. The risk of DRA worsening in patients treated with a combination of a common membrane and a Lixelle column was 5.4% of the risk in patients treated with a common membrane alone (18).

In the same survey, 12 HD patients were treated with Lixelle within one year of developing DRA, and evaluation by physicians indicated improvement in six (50%), no change in five (42%), and worsening in one (8%).

The subjects in the present survey received Lixelle treatment for a mean period of 3.5 ± 2.7 years. The overall symptoms were improved in 56.2%, not changed in 35.1%, and worsened in 8.7% of patients (Fig. 2a). Since the subjects were at a high risk for worsening of DRA because of their long duration of HD (25.9 ± 6.2 years), the outcomes were considered very good (Table 1). Physicians indicated that Lixelle treatment was effective in 251 patients (72.8% of all patients) and partially effective in 83 patients (24.1% of all patients). Of the 251 patients, 181 (72.1%) perceived an improvement in symptoms, 60 (23.9%) perceived no change, and 10 (4.0%) perceived worsening. Of the 83 patients, 12 (14.5%) perceived improvement in symptoms, 53 (63.9%) perceived no improvement, and 18 (21.7%) perceived worsening (Fig. 3).

The patients' evaluation of arthralgia (improved: 53.9%, no change: 40.9%, and worsening: 5.2%) was most similar to their evaluation of overall symptoms (Fig. 2a). This finding suggests that arthralgia is the most important factor in patients' evaluation of disease condition. Patients who did not take analgesics ($n = 167$) evaluated arthralgia as improved (55.5%), unchanged (40.6%), or worsened (3.9%), while these rates for patients with no increase analgesic doses ($n = 330$) were 51.5%, 46.1%, and 2.4%, respectively. Consequently, more than 50% of the patients experienced relief from arthralgia, and at least 40% experienced no change, demonstrating that Lixelle treatment exerts a substantial effect on arthralgia (Fig. 2b). In addition, long-term administration of analgesic NSAIDs and steroids can cause adverse reactions, and they require administration control (19); it is therefore worth noting that analgesic doses were decreased in 23% of the patients.

Arthralgia in bed was improved or unchanged after Lixelle treatment in 96.5% of patients, and the frequency of night-time awakening due to pain in patients with improved arthralgia was significantly lower than that in patients with worsened arthralgia ($P < 0.001$). In the Dialysis Outcomes and Practice Patterns Study (DOPPS), SF-36 self-reported evaluation of sleep quality showed that physical pain was related to sleep quality (20). The results of this survey suggest that Lixelle treatment improved QOL in patients.

Gejyo et al. conducted a small-scale comparative study of a polysulfone dialyzer and a combination of this dialyzer with Lixelle, and found improvements in arthralgia, stiffness, and ADL in the Lixelle group

(14). Lixelle adsorbs and eliminates β2M and decreases β2M modified with AGE, which may reduce inflammation due to activated macrophages. An in vitro study using serum from DRA patients showed that Lixelle also efficiently adsorbed relatively low-molecular-weight (<20 kDa) inflammatory cytokines such as IL-6 and IL-1β (21). Kuragano et al. have reported that Lixelle treatment suppresses bone cyst formation and reduces bone cyst area (15). Although it is not clear whether the adsorption of inflammatory cytokines in circulating blood caused by Lixelle at each HD session contributes to the suppression of local inflammation, this could explain the effectiveness of Lixelle treatment in the suppression of local inflammation and arthralgia.

Hemodialysis with a high-performance membrane also decreases the incidence of carpal tunnel syndrome and bone cysts. The development of DRA depends on the type of the hemodiafiltration method, and this is delayed by the filtration of the dialysate (22–24). However, complete prevention of DRA has yet to be achieved, despite the availability of various high-performance dialyzers and hemodiafiltration methods, and many patients already have DRA. The efficacy of Lixelle treatment in patients diagnosed with DRA by using defined criteria is significant, since it suggests that β2M elimination is the key to inhibiting the progression of DRA and improving QOL in HD patients.

This study had several limitations. Recruitment into this survey was limited to patients who had been receiving Lixelle treatment for at least 9 months, which was considered enough for patients to perceive the treatment effects. Patients who had ceased Lixelle treatment for any reason, including treatment ineffectiveness, were excluded from the survey. Control group responses from these patients might provide a more accurate evaluation of the treatment. Lixelle treatment is applied to each patient on a yearly basis, and the need for another year of treatment is judged annually by temporary discontinuation of treatment. If DRA symptoms disappear after 1 year of treatment and patients do not relapse following discontinuation, or if the treatment is judged to be ineffective, it will cease. Another limitation of this survey is that most of the questions depend on the patients' memory. The average duration of Lixelle treatment is 3.5 ± 2.7 years, with a range from 9 months to 11 years. This duration can affect patients' memories regarding sensory symptoms such as pain and ADL before starting Lixelle treatment. To avoid these limitations and clarify the effectiveness of Lixelle in the practical treatment of DRA, a large-scale cohort study is needed.

CONCLUSIONS

Based on self-evaluation by patients who had been receiving Lixelle treatment, overall dialysis-related amyloidosis symptoms were not worsened in 91% of patients. A similar evaluation by physicians indicated lack of worsening in 97% of cases. These findings suggest that Lixelle treatment arrests the progression of dialysis-related amyloidosis.

Acknowledgments: We would like to express our sincere gratitude to all of the institutions and physicians who participated in this survey.

Contributors: Toshiyuki Date (DATE Clinic), Sadakazu Hisajima (Kushiro Hinyokika Clinic), Yuji Ishida (Ishida Clinic), Noriaki Tanaka (Satellite Clinic Takasago), Hiroshi Yamada (Sakuradai Clinic), Choshu Enatsu (Enatsu Hinyokika Iin), Takasi Yokoyama (Sapporo Tokushukai medical center), Kenzo Kudo (Hamanasu Hospital), Yoshimitsu Kataoka (Miyanomori Memorial Hospital), Shiho Takagawa (Otaru Municipal Medical Center), Shinya Kobayashi (Miyanosawa Urological Clinic), Hajime Yamazaki (Nagaoka Red Cross Hospital), Takayuki Sato (Nanbugo Kosei Hospital), Tatsuya Nonaka (Seishokai Memorial Hospital), Yoshitsugu Tsuchiya (Keijinkai Tsuchiya Clinic), Tomokatsu Saijo (Saijo Clinic Takaban), Masahiko Tozawa (Ikejiriohashi Jin Clinic), Kimiko Otsubo (Sangenjaya Hospital), Yoshihiko Imamura (Nissan Tamagawa Hospital), Takako Suzuki (Moriyama Rehabilitation hospital), Yasuhiro Iguchi (Jisei-Kai Sinsui Clinic), Kazo Kaizu (Yokohama Central Hospital), Takao Suga (Bohsei-Hiratsuka Clinic), Shuzo Kobayashi (ShonanKamakura General Hospital), Tadahiro Nishi (Iryouhoujinshadanhakuzyukai Nishi Clinic), Kimiko Moriyama (Nissin-Ekimae-Clinic), Hajime Ogawa (Ogawa Clinic), Akihiko Chiba (Chiba iin), Tsuguo Sakamoto (Higashiomiya General Hospital), Tetsu Yoshida (Ogawa Hospital), Tetsuya Ooishi (Saiseikai Kurihashi Hospital), Tsuguo Chino (Gengendo Kisarazu Clinic), Katsuhiko Takao (Bouseikai Kisarazu Clinic), Yoichiro Tabata (Toyo Clinic), Shinji Hasegawa (Tokatsu-Clinic, Abiko), Keiji Usui (Kashiwagi Clinic), Seiichi Toyota (SENDAI Jin Hinyokika clinic), Tsuyoshi Yamagishi (Akita Red Cross Hospital), Yoshimi Teramura (Hanazono Hospital), Takasi Sakuma (Sakuma Naika Clinic), Masahiko Ogihara (Ogihara Clinic), Motohiko Aida (Aida Hospital), Hajime Okazaki (Karita Sogo Hospital), Ami Ikeda (Yamagata Saisei Hospital), Mitsuko Matsuzaki (Mitsukaidou Clinic), Hatsuko Yanaka (Shinutsunomiya Clinic), Yasuhiro Sakuma (Ohtawara Red Cross Hospital), Naosaburo Ogata (Ogata Clinic), Masakazu Otsuka (Shimoochiai Clinic), Hisashi Ozasa (Minamiikebukuro Clinic), Hiroshi Kida (Bousei Akabane Clinic), Yuji Nagura (Nihon University Itabashi Hospital), Motoyuki Mugikura (Takashimadaira Central General Hospital), Hideto Emoto (Tokai Hospital), Satoru Kuriyama (Saiseikai Central Hospital), Chizuru Ishiguro (Bousei Nishisinjyuku Clinic), Tsuneo Takenaka (Shinjyuku Suimei Clinic), Masayuki Koshino (Jinken Clinic), Mie Miyashita (Shibuya Park Clinic), Norimasa Yamashita (Yoyogi Yamashita Clinic), Takashi Kasatani (Keiyu Clinic Takanawa), Nobuo Shio (Shio Urological Clinic), Sousyun Hara (Shizuoka Kyoritsu

Clinic), Kazumi Etori (Seirei Numazu Hospital), Kunihiko Miyaji (Miyaji Hospital), Akira Oya (Daido Hospital), Akikazu Yamamoto (Hakuyoukai Hospital), Kimihiro Takayama (Aoi Central Hospital), Shingo Masamoto (Handa Clinic), Satoko Awata (Hekinan Clinic), Masaru Kato (Kamiiida Clinic), Kanako Kojima (Kariya Central Clinic), Kazumasa Usami (Taigenkai Hospital), Tetsushi Esaki (Esaki Clinic), Yasuhiro Sakurauti (Obu Clinic), Hirofumi Oka (Meisei Clinic), Saeko Morikawa (Mikawa Clinic), Shigeki Sawada (Sawada Hospital), Shigeo Hayano (Hayatoku Hospital), Hiroaki Shimosaka (Tajimi Clinic), Hideyuki Takeuchi (Takeuchi Hospital), Yasumasa Kawade (Suzuka Kidney Clinic), Sukenari Koyabu (Owase General Hospital), Etsuo Noda (Sakakibara Onsen Hospital), kei Hirai (Sanko Hospital), Toru Inoue (Osaka Medical College Hospital), Satoshi Ota (Toyama City Hospital), Nobuhisa Shibahara (Arisawa General Hospital), kiyoshi Shozu (Aino Hospital), Akira Kojima (Kojima Clinic), Satoshi Onishi (Yasaka Hospital), Akira Fujimori (Kohnan Hospital), Masato Nishioka (Sumiyoshigawa Hospital), Yoko Inaba (Jikeikai Shin-Suma Hospital), Atsushi Kawai (Chuou Naika Clinic), Isao Kumagai (Teraoka Memorial Hospital), Nobuo Kato (Fukuyama Clinic), Kei Kiribayashi (Clear Yakeyama Clinic), Isao Kusano (Fukushima-naika Clinic), Yasukatsu Michisita (KKR Hokuriku Hospital), Yasuo Kaifu (Kaifu Surgery Clinic), Masatomo Maekawa (Kanazawa Arimatsu Hospital), Yoko Adachi (Shakaihoken Kobe Central Hospital), Haruki Ohue (Ohue Clinic), Takeshi Wakikawa (Osaka Hospital of Japan Seafarers relief Association), Senji Okuno (Shirasagi Clinic), Tadashi Aoki (Nishijin Hospital), Shinji Ono (Mitsubishi Kyoto Hospital), Nobuo Yoshioka (Nishinokyo Hospital), Akifumi Maeda (Kodama Hospital), Takuji Ujita (Ujita Circulation and Internal Medical Clinic), Yoshinobu Yamamoto (Wakaura Central Hospital), Sadako Tamai (Taniguchi Hospital), Keinosuke Kinoshita (Matsuo Surgical Clinic), Hayato Shibaji (Hidaka General Hospital), Motohiro Kamimura (Shingu Municipal Medical Center), Jong II Kim (Cibune Hospital), Kozo Shiraishi (Shiraishi Hospital), Kazuhiro Yano (Kaizuka-Hospital), Michio Ide (St. Mary's Hospital), Satonori Ueyama (Ueyama Hospital), Hidehisa Soejima (Saiseikai Kumamoto Hospital), Nobuhiko Ikezaki (Shinyashiki Clinic), Sadayoshi Ikeda (Otemachi Clinic), Takafumi Shimomura (Ozu Daiichi Clinic), Kenichi Saruwatari (Sankyo Foundation Jinikai Hospital), Etsuo Yoshidome (Seijinkai Ikeda Hospital), Katsuhiko Fukushima (Fukushima Hospital), Ken Shinzato (Shinzato Nephro-Clinic), and Katsushige Abe (Shinzato Clinic).

REFERENCES

1. Gejyo F, Yamada T, Odani S et al. A new form amyloid protein associated with chronic hemodialysis was identified as β2-microglobulin. *Biochem Biophys Res Commun* 1985;129: 701–6.
2. Gejyo F, Odani S, Yamada T et al. β2-microglobulin: a new form of amyloid protein associated with chronic hemodialysis. *Kidney Int* 1986;30:385–90.
3. Gejyo F, Homma N, Arakawa M. Carpal tunnel syndrome and β2-microglobulin-related amyloidosis in chronic hemodialysis patients. *Blood Purif* 1988;6:125–31.
4. Argilés A, Mourad G, Kerr PG et al. Cells surrounding haemodialysis-associated amyloid deposits are mainly macrophages. *Nephrol Dial Transplant* 1994;9:662–7.
5. Inoue H, Saito I, Nakazawa R et al. Expression of inflammatory cytokines and adhesion molecules in haemodialysis-associated amyloidosis. *Nephrol Dial Transplant* 1995;10:2077–82.
6. Miyata T, Oda O, Inagi R et al. β2-microglobulin modified with advanced glycation end products is a major component of hemodialysis-associated amyloidosis. *J Clin Invest* 1993;92: 1243–52.
7. Kleinman KS, Coburn JW. Amyloid syndrome associated with hemodialysis. *Kidney Int* 1989;35:567–75.
8. Dzido G, Sprague SM. Dialysis-related amyloidosis. *Minerva Urol Nefrol* 2003;55:121–9.
9. Lam MF, Tang S, Lai KN. Dialysis-related amyloidosis revisited. *Int J Artif Organs* 2003;26:892–6.
10. Kazama JJ, Yamamoto S, Takahashi N et al. Abeta-2M-amyloidosis and related bone diseases. *J Bone Miner Metab* 2006;24:182–4.
11. Furuyoshi S, Nanko T, Fujiwara S et al. Development of Beta-2-microglobulin adsorbent for direct hemoperfusion. *Jpn J Aphe* 1994;13:152–3.
12. Nakatani M, Furuyoshi S, Takata S et al. Adsorption characteristics of adsorbent column (Lixelle) for the treatment of dialysis-related amyloidosis. *Jpn J Artif Organs* 1998;27:571–7.
13. Abe T, Uchita K, Orita H et al. Effect of β2-microglobulin adsorption column on dialysis-related amyloidosis. *Kidney Int* 2003;64:1522–8.
14. Gejyo F, Kawaguchi Y, Hara S et al. Arresting dialysis-related amyloidosis: a prospective multicenter controlled trial of direct hemoperfusion with a β2-microglobulin adsorption column. *Artif Organs* 2004;28:371–80.
15. Kuragano T, Inoue T, Yoh K et al. Effectiveness of β(2)-microglobulin adsorption column in treating dialysis-related amyloidosis: a multicenter study. *Blood Purif* 2011;32:317–22.
16. Fries JF, Spitz P, Kraines RG et al. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137–45.
17. The Japanese Society of Dialysis Therapy. Overview of regular dialysis treatment in Japan (as of 31 December 1998). *J Jpn Soc Dial Ther* 2000;33:1–27.
18. Nakai S, Iseki K, Tabei K et al. Outcomes of hemodiafiltration based on Japanese dialysis patient registry. *Am J Kidney Dis* 2001;38:S212–6.
19. Bardin T. Low-dose prednisone in dialysis-related amyloid arthropathy. *Rev Rhum* 1994;61:97s–100s.
20. Elder SJ, Pisoni RL, Akizawa T et al. Sleep quality predicts quality of life and mortality risk in haemodialysis patients: results from the dialysis outcomes and practice patterns study (DOPPS). *Nephrol Dial Transplant* 2008;23:998–1004.
21. Tsuchida K, Takemoto Y, Nakamura T et al. Lixelle adsorbent to remove inflammatory cytokines. *Artif Organs* 1998;22: 1064–9.
22. Koda Y, Nishi S, Miyazaki S et al. Switch from conventional to high-flux membrane reduces the risk of carpal tunnel syndrome and mortality of hemodialysis patients. *Kidney Int* 1997; 52:1096–101.
23. Locatelli F, Marcelli D, Conte F et al. Comparison of mortality in ESRD patients on convective and diffusive extracorporeal treatments. The Registro Lombardo Dialisi E Trapianto. *Kidney Int* 1999;55:286–93.
24. Furuya R, Kumagai H, Takahashi M et al. Ultrapure dialysate reduces plasma levels of beta2-microglobulin and pentosidine in hemodialysis patients. *Blood Purif* 2005;23:311–6.

APPENDIX I

The brief result about all of returned questionnaires including that with unanswered items was submitted to *Jin To Touseki* (Japanese Journal, in Japanese) in 2012. We report the final result of the analysis of only fully completed questionnaires in this paper.